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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03029361.7

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Tricyclic imidazoypridines

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Tricyclic Imidazopyridines

Technical field

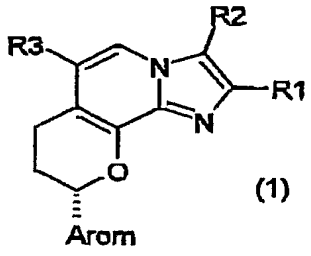
The invention relates to enantiomers of tricyclic imidazopyridines, a process for the preparation of these enantiomers and their use in the pharmaceutical industry as active compounds for preparing medicaments.

Prior Art

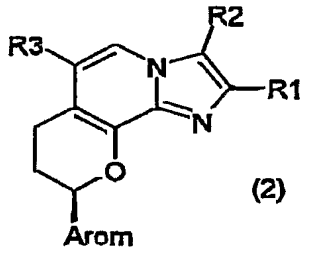
U.S. Patent 4,468,400 describes tricyclic imidazo[1,2-a]pyridines having different ring systems fused to the imidazopyridine skeleton, which compounds are said to be suitable for treating peptide ulcer disorders. The International Patent Applications WO 95/27714, WO 98/42707, WO 98/54188, WO 00/17200, WO 00/26217, WO 00/63211, WO 01/72756, WO 01/72754, WO 01/72755, WO 01/72757, WO 02/34749, WO 03/014120, WO 03/016310, WO 03/014123, WO 03/068774 and WO 03/091253 disclose tricyclic imidazopyridine derivatives having a very specific substitution pattern, which compounds are likewise said to be suitable for treating gastrointestinal disorders.

Description of the Invention

It has now been found that the compounds described for example in WO 03/014123 as racemic mixtures can be separated into their enantiomers or the enantiomers can be prepared in a stereoselective way. It has further been found, unexpectedly, that the enantiomers of the formula 1 have a pronounced activity in inhibiting gastric acid secretion as compared to their optical antipodes of the formula 2.

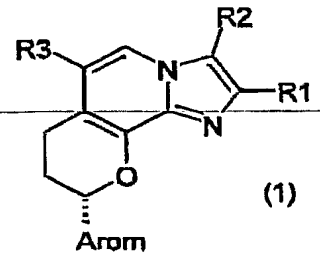


(1)



(2)

The invention thus provides compounds of the formula 1



(1)

where

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl or 1-4C-alkoxycarbonyl

R2 is hydrogen, 1-4C-alkyl, halogen, 2-4C-alkenyl, 2-4C-alkynyl, hydroxy-1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxycarbonyl

R3 is hydroxy-1-2C-alkyl, 1-4C-alkoxy-1-2C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-2C-alkyl, 1-4-C-alkoxycarbonyl or the radical -CO-NR31R32,
where
R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,
or where
R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino, morpholino radical,

Arom is a R4-, R5-, R6- and R7- substituted mono- or bicyclic aromatic radical selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furanyl (furyl), benzofuranyl (benzofuryl), thiophenyl (thienyl), benzothiophenyl (benzothienyl), thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, quinolinyl and isoquinolinyl,
where
R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxyl, aryl, aryl-1-4C-alkyl, aryloxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,
R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,
R6 is hydrogen, 1-4C-alkyl or halogen and
R7 is hydrogen, 1-4C-alkyl or halogen,
where
aryl is phenyl or substituted phenyl having one, two or three identical or different substituents from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxyl and cyano,

and the salts of these compounds.

1-4C-Alkyl denotes straight-chain or branched alkyl radicals having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

3-7C-Cycloalkyl denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, among which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

1-4C-Alkoxy denotes radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

1-4C-Alkoxy-1-4C-alkyl denotes one of the abovementioned 1-4C-alkyl radicals which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxymethyl, the methoxyethyl and the butoxyethyl radicals.

1-4C-Alkoxycarbonyl (-CO-1-4C-alkoxy) denotes a carbonyl group to which is attached one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxycarbonyl (CH_3O-C(O)-) and the ethoxycarbonyl (CH_3CH_2O-C(O)-) radicals.

For the purpose of the invention, halogen is bromine, chlorine and fluorine.

2-4C-Alkenyl denotes straight-chain or branched alkenyl radicals having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butenyl, 3-butenyl, 1-propenyl and the 2-propenyl (allyl) radicals.

2-4C-Alkynyl denotes straight-chain or branched alkynyl radicals having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butynyl, the 3-butynyl, 2-propynyl (propargyl) and, preferably, the 1-ethynyl, 1-propynyl and 1-butynyl radicals.

Hydroxy-1-4C-alkyl denotes abovementioned 1-4C-alkyl radicals which are substituted by a hydroxyl group. Examples which may be mentioned are the hydroxymethyl, the 2-hydroxyethyl and the 3-hydroxypropyl radicals.

1-2C-Alkyl denotes the methyl or the ethyl radicals.

Hydroxy-1-2C-alkyl denotes abovementioned 1-2C-alkyl radicals which are substituted by a hydroxyl group. Examples which may be mentioned are the hydroxymethyl and the 2-hydroxyethyl radicals.

1-4C-Alkoxy-1-2C-alkyl denotes one of the abovementioned 1-2C-alkyl radicals which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxymethyl, the methoxyethyl and the butoxyethyl radicals.

1-4C-Alkoxy-1-4C-alkoxy denotes one of the abovementioned 1-4C-alkoxy radicals which is substituted by a further 1-4C-alkoxy radical. Examples which may be mentioned are the radicals 2-(methoxy)ethoxy (CH_3-O-CH_2-CH_2-O-) and 2-(ethoxy)ethoxy (CH_3-CH_2-O-CH_2-CH_2-O-).

1-4C-Alkoxy-1-4C-alkoxy-1-2C-alkyl denotes one of the abovementioned 1-4C-alkoxy-1-2C-alkyl radicals which is substituted by one of the abovementioned 1-4C-alkoxy radicals. An example which may be mentioned is the radical 2-(methoxy)ethoxymethyl (CH_3-O-CH_2-CH_2-O-CH_2-).

1-7C-Alkyl denotes straight-chain or branched alkyl radicals having 1 to 7 carbon atoms. Examples which may be mentioned are the heptyl, isoheptyl-(5-methylhexyl), hexyl, isohexyl-(4-methylpentyl), neohexyl-(3,3-dimethylbutyl), pentyl, isopentyl-(3-methylbutyl), neopentyl-(2,2-dimethylpropyl), butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

Carboxy-1-4C-alkyl denotes, for example, the carboxymethyl (-CH_2COOH) or the carboxyethyl (-CH_2CH_2COOH) radical.

1-4C-Alkoxycarbonyl-1-4C-alkyl denotes one of the abovementioned 1-4C-alkyl radicals which is substituted by one of the abovementioned 1-4C-alkoxycarbonyl radicals. An example which may be mentioned is the ethoxycarbonylmethyl (CH_3CH_2OC(O)CH_2-) radical.

Aryl-1-4C-alkyl denotes an aryl-substituted 1-4C-alkyl radical. An example which may be mentioned is the benzyl radical.

Aryl-1-4C-alkoxy denotes an aryl-substituted 1-4C-alkoxy radical. An example which may be mentioned is the benzyloxy radical.

Mono- or di-1-4C-alkylamino radicals contain, in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Preference is given to di-1-4C-alkylamino and in particular to dimethyl-, diethyl- or diisopropylamino.

1-4C-Alkylcarbonylamino denotes an amino group to which a 1-4C-alkylcarbonyl radical is attached. Examples which may be mentioned are the propionylamino (C_3H_7C(O)NH-) and the acetylamino (acetamido, CH_3C(O)NH-) radicals.

1-4C-Alkoxycarbonylamino denotes an amino radical which is substituted by one of the abovementioned 1-4C-alkoxycarbonyl radicals. Examples which may be mentioned are the ethoxycarbonylamino and the methoxycarbonylamino radicals.

1-4C-Alkoxy-1-4C-alkoxycarbonyl denotes a carbonyl group to which one of the abovementioned 1-4C-alkoxy-1-4C-alkoxy radicals is attached. Examples which may be mentioned are the 2-(methoxy)-ethoxycarbonyl (CH_3-O-CH_2CH_2-O-CO-) and the 2-(ethoxy)ethoxycarbonyl (CH_3CH_2-O-CH_2CH_2-O-CO-) radicals.

1-4C-Alkoxy-1-4C-alkoxycarbonylamino denotes an amino radical which is substituted by one of the abovementioned 1-4C-alkoxy-1-4C-alkoxycarbonyl radicals. Examples which may be mentioned are the 2-(methoxy)ethoxycarbonylamino and the 2-(ethoxy)ethoxycarbonylamino radicals.

Radicals Arom which may be mentioned are, for example, the following substituents: 4-acetoxyphenyl, 4-acetamidophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 3-benzyloxy-4-methoxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3,5-bis(trifluoromethyl)phenyl, 4-butoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-chloro-6-fluorophenyl, 3-chloro-4-fluorophenyl, 2-chloro-5-nitrophenyl, 4-chloro-3-nitrophenyl, 3-(4-chlorophenoxy)phenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 2,4-dihydroxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxy-5-hydroxyphenyl, 2,5-dimethylphenyl, 3-ethoxy-4-hydroxyphenyl, 2-fluorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 2-hydroxy-5-nitrophenyl, 3-methoxy-2-nitrophenyl, 3-nitrophenyl, 2,3,5-trichlorophenyl, 2,4,6-trihydroxyphenyl, 2,3,4-trimethoxyphenyl, 2-hydroxy-1-naphthyl, 2-methoxy-1-naphthyl, 4-methoxy-1-naphthyl, 1-methyl-2-pyrrolyl, 2-pyrrolyl, 3-methyl-2-pyrrolyl, 3,4-dimethyl-2-pyrrolyl, 4-(2-methoxycarbonylethyl)-3-methyl-2-pyrrolyl, 5-ethoxycarbonyl-2,4-dimethyl-3-pyrrolyl, 3,4-dibromo-5-methyl-2-pyrrolyl, 2,5-dimethyl-1-phenyl-3-pyrrolyl, 5-carboxy-3-ethyl-4-methyl-2-pyrrolyl, 3,5-dimethyl-2-pyrrolyl, 2,5-dimethyl-1-(4-trifluoromethylphenyl)-3-pyrrolyl, 1-(2,6-dichloro-4-trifluoromethylphenyl)-2-pyrrolyl, 1-(2-nitrobenzyl)-2-pyrrolyl, 1-(2-fluorophenyl)-2-pyrrolyl, 1-(4-trifluoromethoxyphenyl)-2-pyrrolyl, 1-(2-nitrobenzyl)-2-pyrrolyl, 1-(4-ethoxycarbonyl)-2,5-dimethyl-3-pyrrolyl, 5-chloro-1,3-dimethyl-4-pyrazolyl, 5-chloro-1-methyl-3-trifluoromethyl-4-pyrazolyl, 1-(4-chlorobenzyl)-5-pyrazolyl, 1,3-dimethyl-5-(4-chlorophenoxy)-4-pyrazolyl, 1-methyl-3-trifluoromethyl-5-(3-trifluoromethylphenoxy)-4-pyrazolyl, 4-methoxycarbonyl-1-(2,6-dichlorophenyl)-5-pyrazolyl, 5-allyloxy-1-methyl-3-trifluoromethyl-4-pyrazolyl, 5-chloro-1-phenyl-3-trifluoromethyl-4-pyrazolyl, 3,5-dimethyl-1-phenyl-4-imidazolyl, 4-bromo-1-methyl-5-imidazolyl, 2-butylimidazolyl, 1-phenyl-1,2,3-triazol-4-yl, 3-indolyl, 4-indolyl, 7-indolyl, 5-methoxy-3-indolyl, 5-benzyloxy-3-indolyl, 1-benzyl-3-indolyl, 2-(4-chlorophenyl)-3-indolyl, 7-benzyloxy-3-indolyl, 6-benzyloxy-3-indolyl, 2-methyl-5-nitro-3-indolyl, 4,5,6,7-tetrafluoro-3-indolyl, 1-(3,5-difluorobenzyl)-3-indolyl, 1-methyl-2-(4-trifluorophenoxy)-3-indolyl, 1-methyl-2-benzimidazolyl, 5-nitro-2-furyl, 5-hydroxymethyl-2-furyl, 2-furyl, 3-furyl, 5-(2-nitro-4-trifluoromethylphenyl)-2-furyl, 4-ethoxycarbonyl-5-methyl-2-furyl, 5-(2-trifluoromethoxyphenyl)-2-furyl, 5-(4-methoxy-2-nitrophenyl)-2-furyl, 4-bromo-2-furyl, 5-dimethylamino-2-furyl, 5-bromo-2-furyl, 5-sulfo-2-furyl, 2-benzofuryl, 2-thienyl, 3-thienyl, 3-methyl-2-thienyl, 4-bromo-

2-thienyl, 5-bromo-2-thienyl, 5-nitro-2-thienyl, 5-methyl-2-thienyl, 5-(4-methoxyphenyl)-2-thienyl, 4-methyl-2-thienyl, 3-phenoxy-2-thienyl, 5-carboxy-2-thienyl, 2,5-dichloro-3-thienyl, 3-methoxy-2-thienyl, 2-benzothienyl, 3-methyl-2-benzothienyl, 2-bromo-5-chloro-3-benzothienyl, 2-thiazolyl, 2-amino-4-chloro-5-thiazolyl, 2,4-dichloro-5-thiazolyl, 2-diethylamino-5-thiazolyl, 3-methyl-4-nitro-5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 6-methyl-2-pyridyl, 3-hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl, 2,6-dichloro-4-pyridyl, 3-chloro-5-trifluoromethyl-2-pyridyl, 4,6-dimethyl-2-pyridyl, 4-(4-chlorophenyl)-3-pyridyl, 2-chloro-5-methoxycarbonyl-6-methyl-4-phenyl-3-pyridyl, 2-chloro-3-pyridyl, 6-(3-trifluoromethylphenoxy)-3-pyridyl, 2-(4-chlorophenoxy)-3-pyridyl, 2,4-dimethoxy-5-pyrimidine, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 2-chloro-3-quinolinyl, 2-chloro-6-methoxy-3-quinolinyl, 8-hydroxy-2-quinolinyl and 4-isoquinolinyl.

Suitable salts of compounds of the formula 1 are – depending on the substitution – in particular all acid addition salts. Particular mention may be made of the pharmacologically acceptable salts of the inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, where the acids are employed in the salt preparation in an equimolar ratio or in a ratio differing therefrom, depending on whether the acid is a mono- or polybasic acid and on which salt is desired.

Pharmacologically unacceptable salts, which can be initially obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically acceptable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention and their salts can, for example when they are isolated in crystalline form, comprise varying amounts of solvents. The invention therefore also embraces all solvates and, in particular, all hydrates of the compounds of the formula 1, and all solvates and, in particular, all hydrates of the salts of the compounds of the formula 1.

Compounds which are to be emphasized are those compounds of the formula 1, where

R1 is 1-4C-alkyl or 3-7C-cycloalkyl

R2 is 1-4C-alkyl, halogen, hydroxy-1-4C-alkyl, 2-4C-alkenyl or 3-7C-cycloalkyl,

R3 is the radical -CO-NR31R32,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino, morpholino radical,

Arom is a R4-, R5-, R6- and R7- substituted mono- or bicyclic aromatic radical selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furanyl (furyl), benzofuranyl (benzofuryl), thiophenyl (thienyl), benzothiophenyl (benzothienyl), thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, quinolinyl and isoquinolinyl,

where

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxyl, aryl, aryl-1-4C-alkyl, aryloxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,

R6 is hydrogen, 1-4C-alkyl or halogen and

R7 is hydrogen, 1-4C-alkyl or halogen,

where

aryl is phenyl or substituted phenyl having one, two or three identical or different substituents from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxyl and cyano,

and the salts of these compounds.

Emphasis is given to compounds of the formula 1, where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl, halogen, hydroxy-1-4C-alkyl or 2-4C-alkenyl,

R3 is the radical -CO-NR31R32,

where

R31 is hydrogen or 1-7C-alkyl,

R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino, morpholino radical,

Arom is a R4- and R5- substituted phenyl, furanyl (furyl), thiophenyl (thienyl) or pyridinyl,

where

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,

and the salts of these compounds.

Particular emphasis is given to compounds of the formula 1, where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is the radical -CO-NR31R32,

where

R31 is hydrogen or 1-7C-alkyl,

R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino, morpholino radical,

Arom is a R4- and R5- substituted phenyl, furanyl (furyl), thiophenyl (thienyl) or pyridinyl,

where

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,

and the salts of these compounds.

Particular emphasis is also given to compounds of the formula 1, where

R1 is 1-4C-alkyl,

R2 halogen, hydroxy-1-4C-alkyl or 2-4C-alkenyl,

R3 is the radical -CO-NR31R32,

where

R31 is hydrogen or 1-7C-alkyl,

R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino, morpholino radical,

Arom is a R4- and R5- substituted phenyl, furanyl (furyl), thiophenyl (thienyl) or pyridinyl,

where

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,

and the salts of these compounds.

Particular emphasis is also given to compounds of the formula 1 where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is the radical -CO-NR31R32,

where

R31 is hydrogen or 1-7C-alkyl,

R32 is hydrogen or 1-7C-alkyl,

Arom is phenyl

and the salts of these compounds.

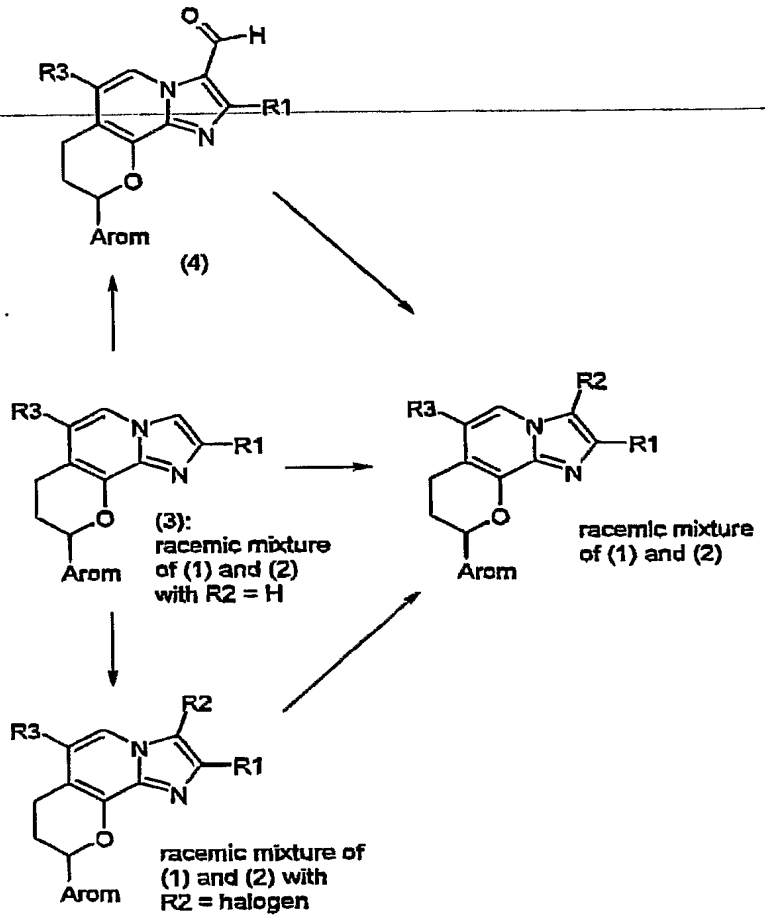
The following examplary compounds of the formula 1 can be synthesized according the general procedures outlined in more detail below:

R1	R2	R3	Arom
CH_3	CH_3	-C(O)-N(H)CH_3	phenyl
CH_3	CH_3	-C(O)-NH_2	phenyl
CH_3	CH_3	-C(O)-pyrrolidino	phenyl
CH_3	CH_3	-C(O)-N$(CH_3)_2$	phenyl
CH_3	Br	-C(O)-N$(CH_3)_2$	phenyl
CH_3	-CH_2OH	-C(O)-N$(CH_3)_2$	phenyl
CH_3	-CH=CH_2	-C(O)-N$(CH_3)_2$	phenyl
CH_3	-CH_2CH_3	-C(O)-N$(CH_3)_2$	phenyl

The compounds according to the invention can be prepared from the corresponding racemic mixtures by separating the desired compound of the formula 1 from its optical antipode of the formula 2 by techniques known to the expert. The separation can be achieved for example by crystallization of diastereomeric salts after reaction of the racemic mixture of acid free compounds of the formula 1 and of the formula 2 with a suitable, optically pure acid or by preparative chromatography using a chiral column. The racemic mixtures of compounds of the formula 1 and of the formula 2, preferably those in which R2 is 1-4C-alkyl, for this purpose can be obtained as described for example in WO 03/014123 or by analogous reaction steps.

Alternatively racemic mixtures of compounds of the formula 1 and compounds of the formula 2, preferably those in which R2 is hydrogen, halogen, 2-4C-alkenyl, 2-4C-alkynyl, hydroxy-1-4C-alkyl, 3-7C-cycloalkyl or 1-4C-alkoxycarbonyl, can be prepared for example as outlined in the schemes 1, 2 and 3, which follow.

Scheme 1:



Compounds of the formula 3 can be transformed directly to a racemic mixture of compounds of the formula 1 and compounds of the formula 2, for example by electrophilic aromatic substitution. One example to be mentioned is an aminomethylation reaction.

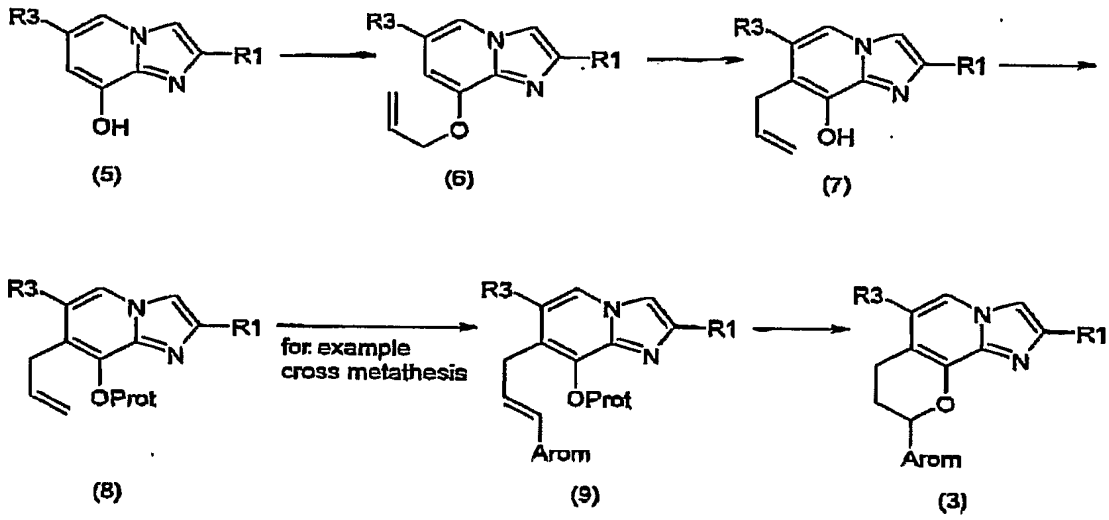
Alternatively, compounds of the formula 3 can be first transformed, for example by a Vilsmeier formylation, to compounds of the formula 4, followed by further derivatization reactions, which are known to the expert (for example reduction of the aldehyde group, followed if desired by an etherification, or oxidation of the aldehyde group, followed by esterification or amide formation), to a racemic mixture of compounds of the formula 1 and compounds of the formula 2.

Another possible access to a racemic mixture of compounds of the formula 1 and compounds of the formula 2 is, for example, offered by the transformation of a racemic mixture of compounds of the formula 1 and compounds of the formula 2 with R2 = halogen, for example by C-C-bond forming reactions, like for example Heck-, Suzuki- or Sonogashira-coupling reactions. A racemic mixture of compounds of the formula 1 and compounds of the formula 2 with R2 = halogen can be prepared from

compounds of the formula 3 for example by a halogenation reaction, for example a bromination reaction using a bromination reagent, like for example N-bromosuccinimide.

Compounds of the formula 3 can be prepared, for example according to the reaction sequence outlined in scheme 2.

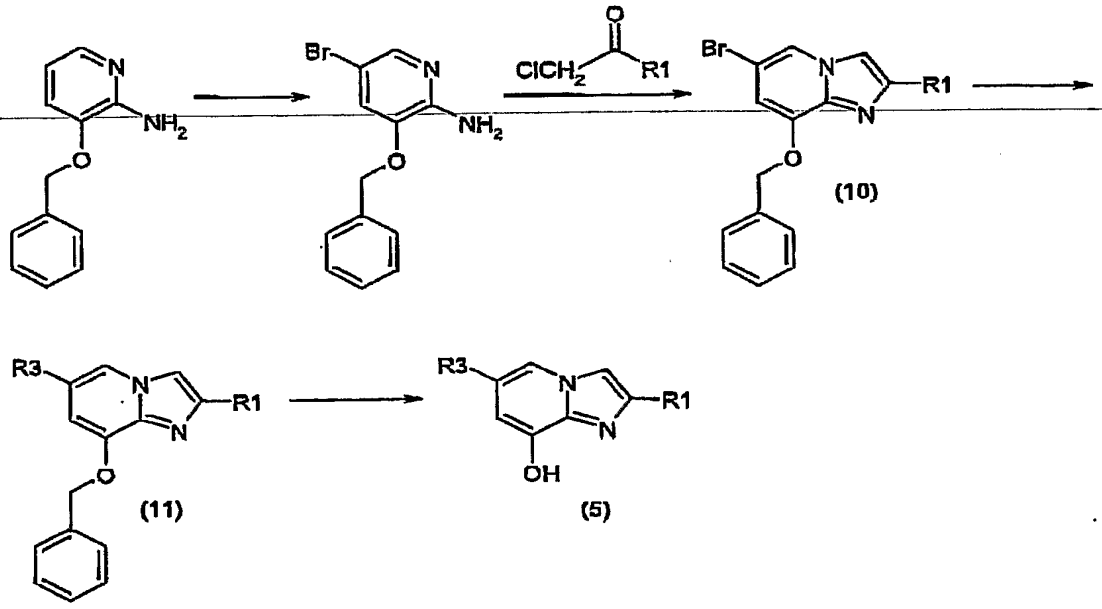
Scheme 2



Compounds of the formula 7 can be obtained for example from compounds of the formula 5 by an O-alkylation followed by a thermally induced Claisen-rearrangement reaction of the O-alkylation product of the formula 6. Protection of the alcohol functionality in compounds of the formula 7 with a suitable protection group Prot, for example a pivaloyl group, using standard conditions leads to compounds of the formula 8, which can be subjected in a next reaction step for example to a cross metathesis reaction, for example using a suitable Grubbs catalyst, suitable for the introduction of the Arom residue. The reaction products of the formula 9 can be deprotected and the ring closure can be performed using methods known to the expert, for example under acidic conditions, which leads to the desired compounds of the formula 3.

Compounds of the formula 5 can be prepared in analogy to the procedure described in WO 03/014123, for example as outlined in an exemplary manner in scheme 3.

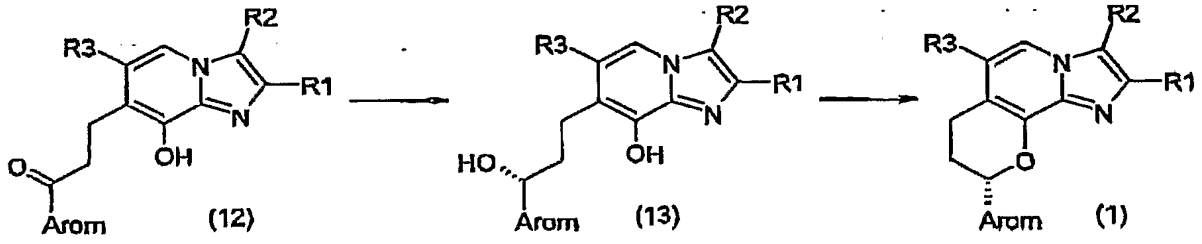
Scheme 3



The preparation of compounds of the formula 11 from compounds of the formula 10 is carried out in a manner known per se to the person skilled in the art, for example in analogy to the reactions described in an exemplary manner in the International Patent Application WO 03/014123. Hydrogenation of compounds of the formula 11 to compounds of the formula 5 is carried out in a manner known per se to the person skilled in the art, using standard reaction conditions, like for example using hydrogen / Pd(0).

Alternatively compounds of the formula 1 can be prepared in a stereoselective way following the reaction steps as outlined generally in scheme 4. Compounds of the formula 13 can be prepared from compounds of the formula 12 by an asymmetric hydrogenation using a chiral hydrogenation catalyst like for example Ruthenium catalysts as described by Noyori et. al. in *Angew. Chem.* **2001**, *113*, 40-75.

Scheme 4



Compounds of the formula 12 are known for example from WO 03/014123, or they can be prepared in a known manner, analogously to known compounds. The purity of the compounds of the formula 12 has a major impact on the reaction conditions and the outcome of the asymmetric catalytic hydrogena-

tion. In contrast to WO 03/014123 a further purification step is required, for example a crystallization step in the presence of a suitable organic acid, as described in an exemplary manner in the examples.

The derivatization, if any, of the compounds obtained according to the above Schemes 1, 2, 3 and 4 (e.g. conversion of a group R3 into another group R3 or conversion of a group R2 into another group R2) is likewise carried out in a manner known to the expert. For example, if compounds where R2 and/or R3 = -CO-1-4C-alkoxy, or where R2 and/or R3 = -CO-NR31R32 are desired, an appropriate derivatization can be performed in a manner known to the expert (e. g. metal catalysed carbonylation of the corresponding halo compound or conversion of an ester into an amide) at the stage of the compounds of formula 3, 5 or 12 (schemes 2, 3 and 4) or more conveniently at a later point in time, for example conversion of a compound of the formula 1 into another compound of the formula 1.

The examples below serve to illustrate the invention in more detail without limiting it. Further compounds of the formula 1 whose preparation is not described explicitly can likewise be prepared in an analogous manner or in a manner known per se to the person skilled in the art, using customary process techniques. The abbreviation min stands for minute(s), h stands for hour(s), m.p. stands for melting point and ee for enantiomeric excess.

Furthermore the following abbreviations are used for the chemical substances indicated:

(*S*)-BINAP	(*S*)-2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl
(S)-DAIPEN	(2S)-(+)-1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine
(S,S)-DIPEN	(1*S*,2*S*)-(-)-1,2-diphenylethylene diamine
(*S*)-(+)-MTPACl	(*S*)-(+)-α-methoxy-α-(trifluormethyl)phenylacetyl chloride
DIAD	diisopropyl azodicarboxylate

Examples

I. Compounds of the formula 1

1. (8*S*)-2,3-Dimethyl-8-phenyl-7,8-dihydro-6H-9-oxa-1,3a-diaza-cyclopenta[a]naphthalene-5-carboxylic acid dimethylamide (*R*,*R*)-tartrate

By application of heat, racemic 2,3-Dimethyl-8-phenyl-7,8-dihydro-6H-9-oxa-1,3a-diaza-cyclopenta[a]naphthalene-5-carboxylic acid dimethylamide (840 mg, 2.40 mmol) and L-(+)-tartaric acid (358 mg, 2.39 mmol) were dissolved in isopropanol (5 ml) and water (5 ml). The mixture was allowed to crystallize for 2 days at room temperature. The precipitate formed (700 mg) was isolated and the enantiomeric excess was determined by chiral HPLC analysis (cf. below, 21 % ee). Recrystallization of the solid from a mixture of isopropanol and water [1:1 (v/v), 14 ml] afforded three crops of crystals: first crop: 30 mg, 73 % ee; second crop: 120 mg, 67 % ee; third crop: yield and ee not determined. The first two crops were combined and recrystallized from isopropanol/water [1:1 (v/v), 3 ml]. An ee value of 88 % was determined for the isolated salt (60 mg). This sample was again crystallized from isopropanol/water [1:1 (v/v), 2 ml] yielding a pure sample of the title compound (4 mg, 0.3 % yield, 95 % ee). The third crop of the crystallization mentioned above was added to the mother liquor and another 23 mg of the title compound (91 % ee) were isolated by crystallization. Recrystallization of this sample from isopropanol/water [1:1 (v/v), 0.4 ml] afforded the title compound with 96% ee (10 mg, 0.8 % yield).

The enantiomeric excess was determined by HPLC analysis employing the following conditions: column: Chiralcel OJ; solvent system: heptane / ethanol / diethylamine = 90:10:0.2 (v/v/v); flow rate: 1.0 ml/min; temperature: 40 °C. The (8*R*)-enantiomer showed a retention time of 15.5 min, the (8*S*)-enantiomer (title compound) was eluted after 18.4 min.

^{1}H-NMR (dmso-d_6, 400 MHz): δ = 2.12 (m_c, 1H), 2.25 (s, bs, 4 H), 2.34 (s, 3 H), 2.49 (bs), 2.75 (m_c, 1 H), 2.86, 3.00 (2 s, 6 H), 4.24 (s, 2 H), 5.26 (d, 1 H), 7.40 (m_c, 5 H), 7.80 (s, 1 H).

2. (8*S*)-2,3-Dimethyl-8-phenyl-7,8-dihydro-6H-9-oxa-1,3a-diaza-cyclopenta[a]naphthalene-5-carboxylic acid dimethylamide

Resolution of racemic 2,3-Dimethyl-8-phenyl-7,8-dihydro-6H-9-oxa-1,3a-diaza-cyclopenta[a]naphthalene-5-carboxylic acid dimethylamide (3.00 g, 8.6 mmol) was achieved by preparative chromatography using a 250 x 110 mm CHIRALPAK® AD 20 µm column. The mobile phase consisted of a mixture of ethanol, methanol, and diethylamine [50:50:0.1 (v/v/v)]. The separation was performed at room temperature with a flow rate of 500 ml/min. The products were detected at a wavelength of 300 nm. The second-eluting enantiomer was identified as the title compound ((8*S*)-enantiomer) (1.38 g, 46 % yield, 98.7 % ee, m. p.: 254 °C).

The set-up of the analytical method for the determination of the optical purity was as follows: column: combination of 250 x 4.6 mm CHIRALPAK® AD and 250 x 4.6 mm CHIRALPAK® AD-H; mobile phase: ethanol, methanol, diethylamine [50:50:0.1 (v/v/v)]; flow rate: 1 ml/min; room temperature. The title compound was eluted after 9.0 min.

The optical purity was also examined by means of optical rotation: For the title compound ((8*S*)-enantiomer) an $[\alpha]^{D}_{20}$ value of -53° (c = 0.63, dichloromethane) was determined.

3. (8*S*)-2,3-Dimethyl-8-phenyl-7,8-dihydro-6H-9-oxa-1,3a-diaza-cylopenta[a]naphthalene-5-carboxylic acid dimethylamide prepared by asymmetric synthesis

In a flame-dried flask filled with argon, the diol 8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide [starting material b, prepared by asymmetric hydrogenation; ratio of enantiomers (3*S*) / (3*R*) = 5:95, 300 mg, 0.82 mmol] was dissolved in dry THF (18 ml). After addition of triphenylphosphine (640 mg, 2.44 mmol) and DIAD (500 mg, 487 µl, 2.48 mmol) the reaction mixture was stirred for 2 h at room temperature. The clear solution was then poured onto a mixture of saturated ammonium chloride solution (10 ml) and ethyl acetate (15 ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (8 ml). The organic phases were washed with saturated ammonium chloride solution (10 ml) and water (10 ml), dried over sodium sulfate, and evaporated to dryness. The crude product was purified by flash chromatography [30 g of silica gel, solvent: ethyl acetate / methanol = 20:1 (v/v)] and subsequent washing with diethyl ether. A colourless solid (m. p.: 259-261 °C) was obtained (70 mg, 25 %), the title compound ((8*S*)-enantiomer) and its enantiomer ((8*R*)-enantiomer) free of by-products, as confirmed by ^{1}H-NMR spectroscopy. The optical purity was determined by chiral HPLC: column: CHIRALPAK® AD-H 250 x 4.6 mm, 5 µm; solvent: ethanol/methanol = 1:1 (v/v) with 0.1 % of diethylamine, flow rate: 1 ml/min; temperature: 35 °C. The (8*R*)-enantiomer (5.17 area-%) and the (8*S*)-enantiomer (94.83 area-%) were eluted at retention times of 3.99 min / 4.38 min, respectively. Thus, the enantiomeric excess of 90 % ee was conserved in the course of the Mitsunobu etherification.

II. Compounds of the formula 2

A. (8*R*)-2,3-Dimethyl-8-phenyl-7,8-dihydro-6H-9-oxa-1,3a-diaza-cylopenta[a]naphthalene-5-carboxylic acid dimethylamide (*S,S*)-tartrate

By application of heat, racemic 2,3-dimethyl-8-phenyl-7,8-dihydro-6H-9-oxa-1,3a-diaza-cylopenta[a]naphthalene-5-carboxylic acid dimethylamide (840 mg, 2.40 mmol) and L-(+)-tartaric acid (358 mg, 2.39 mmol) were dissolved in isopropanol (5 ml) and water (5 ml). The mixture was allowed to crystallize for 2 days at room temperature. After removal of the precipitate, the mother liquor was concentrated, treated with 1 N NaOH (40 ml), and extracted with a mixture of ethyl acetate / methanol [95:5 (v/v), 3 x 150 ml]. The combined organic phases were washed with brine (75 ml), dried over sodium sulfate and concentrated under reduced pressure. Thus, a sample of 2,3-Dimethyl-8-phenyl-

7,8-dihydro-6H-9-oxa-1,3a-diaza-cyclopenta[a]naphthalene-5-carboxylic acid dimethylamide containing an excess of the (8*R*)-enantiomer (250 mg, 31 % ee) was isolated which was dissolved in isopropanol (4 ml) and water (4 ml). D-(-)-tartaric acid (107 mg, 0.71 mmol) was added and the mixture was allowed to crystallize. The precipitate was isolated (75 mg, 79 % ee) and recrystallized from isopropanol/water [1:1 (v/v), 2 ml]. This afforded 14 mg (1.1 %) of the title compound (enantiomeric excess > 90 %).

The enantiomeric excess was determined by HPLC analysis employing the following conditions: column: Chiralcel OJ; solvent system: heptane / ethanol / diethylamine = 90:10:0.2 (v/v/v); flow rate: 1.0 ml/min; temperature: 40 °C. The (8*R*)-enantiomer (title compound) showed a retention time of 15.5 min, the (8*S*)-enantiomer (example 1) was eluted after 19.1 min.

^{1}H-NMR (dmso-d_6, 400 MHz): δ = 2.12 (m_c, 1H), 2.25 (s, bs, 4 H), 2.34 (s, 3 H), 2.49 (bs), 2.75 (m_c, 1 H), 2.86, 3.00 (2 s, 6 H), 4.23 (s, 2 H), 5.26 (d, 1 H), 7.41 (m_c, 5 H), 7.80 (s, 1 H).

B. (8*R*)-2,3-Dimethyl-8-phenyl-7,8-dihydro-6H-9-oxa-1,3a-diaza-cyclopenta[a]naphthalene-5-carboxylic acid dimethylamide

The isolation of the (8*R*)-enantiomer was performed as described in example 2 with the first-eluting enantiomer being the title compound. 1.40 g (47 % yield, 98.2 % ee) of the title compound (m.p. 254 °C) were obtained from 3.00 g (8.6 mmol) of racemic mixture. The $[\alpha]^{D}_{20}$ value measured for the title compound ((8*R*)-enantiomer) was 53 ° (*c* = 0.61, dichloromethane). Under the analytical HPLC conditions described in example 2, the title compound showed a retention time of 8.0 min.

III. Starting Materials

a. 8-Hydroxy-2,3-dimethyl-7-(3-oxo-3-phenyl-propyl)-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide

(a) In a flame-dried flask filled with argon, a suspension of the alcohol 8-Hydroxy-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide (50.0 g, 214 mmol) in dry dichloromethane (1.2 l) was treated with *N,N*-dimethylmethylenimmonium iodide (40.3 g, 218 mmol). The reaction mixture was stirred for 1 h at room temperature. In the beginning, a clear solution was obtained, within 10 minutes the formation of a precipitate was observed. The solvent was then removed under reduced pressure.

(b) The rotary evaporator was filled with argon, the colourless solid (7-Dimethylaminomethyl-6-dimethylcarbamoyl-8-hydroxy-2,3-dimethyl-imidazo[1,2-a]pyridin-1-ium; iodide) was dried *in vacuoo*, and was dissolved in dry DMF (1.1 l) which had been pre-heated to 50 °C. An almost clear solution was obtained, which was treated with potassium carbonate (30.4 g, 220 mmol) and acetophenone pyrrolidine enamine (82.5 g, purity: 90 weight-%, 428 mmol). In a pre-heated oil bath, the brown solu-

tion was stirred for 30 minutes at 50 °C and was then poured onto a stirred mixture of ammonium chloride (130 g), water (200 ml), ice (300 g), and dichloromethane (600 ml). Stirring was continued for several minutes and the pH-value was adjusted to pH = 8 by addition of 6N hydrochloric acid. The phases were separated and the aqueous phase was extracted with dichloromethane (3 x 100 ml). The combined organic phases were washed with water (2 x 100 ml), dried over sodium sulfate and concentrated under reduced pressure (DMF was removed at a temperature of 60 °C). A dark-brown oily residue (80 g) was obtained which was dried *in vacuoo*.

(c) The residue (crude title compound) was purified by filtration over silica gel [500 g, solvent: ethyl acetate (removal of acetophenone formed by cleavage of excess enamine), then ethyl acetate / methanol = 8:2 (v/v)]. A red brown solid was isolated (60 g of crude title compound, HPLC-purity: 88.08 %) which was dried *in vacuoo*, dissolved in methanol (200 ml), and treated with fumaric acid (25.5 g, 220 mmol). The brown suspension was stirred for 20 min at 40 °C, at which point a clear solution was obtained. The solution was concentrated under reduced pressure until a dense suspension was formed. Acetone (120 ml) was added and the mixture was concentrated again until a dense suspension was formed. The slurry was diluted with acetone (150 ml) and was stirred at 40 °C (30 min), room temperature (19 h), and at 0 °C (2 h). The precipitate, which was formed, was removed by filtration, washed with acetone (20 ml) and diethyl ether (50 ml), and dried *in vacuoo*. A colourless solid (51 g, 49 % yield, melting point: 196-198 °C, HPLC-purity: 98.24 %) was obtained which was characterized by ^{1}H NMR spectroscopy to be the salt of the title compound and fumaric acid in a molar ratio of 1:1.

(d) The salt of the title compound and fumaric acid (50 g, 104 mmol) was added portion-wise to a mixture of sodium bicarbonate (42 g, 500 mmol), water (400 ml), and dichloromethane (400 ml). The biphasic mixture was stirred for 5 minutes. The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 50 ml). The organic phases were washed with water (2 x 100 ml), dried over sodium sulfate, and concentrated under reduced pressure. A colourless, foamy solid was isolated, which was characterized as the title compound (37.7 g, 99 % yield, 49 % overall yield). The sample was pure by means of ^{1}H-NMR spectroscopy and showed an HPLC purity of 99.07 %.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 2.32, 2.37 (2 s, 6 H), 2.95 (s), 3.05 (bs), 3.14 (s, Σ 8 H), 3.42 (m_c, 2 H), 7.29 (s, 1 H), 7.47 (m_c, 3 H), 8.00 (m_c, 2 H).

b. 8-Hydroxy-7-[(3*R*)-3-hydroxy-3-phenyl-propyl]-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide; prepared by asymmetric catalytic hydrogenation

In a flame-dried flask filled with argon, the ketone 8-Hydroxy-2,3-dimethyl-7-(3-oxo-3-phenyl-propyl)-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide (1.00 g, 2.7 mmol) was suspended in dry isopropanol (80 ml), which had been degassed with argon. After addition of potassium *tert*-butylate (0.37 g, 3.0 mmol), a yellow solution was obtained which was treated with the hydrogenation catalyst $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN] (catalyst is commercially available from Strem Chemicals, Newburyport, MA, USA) (152 mg, 0.14 mmol, 5 mol-%). The reaction mixture was transferred into a 300 ml

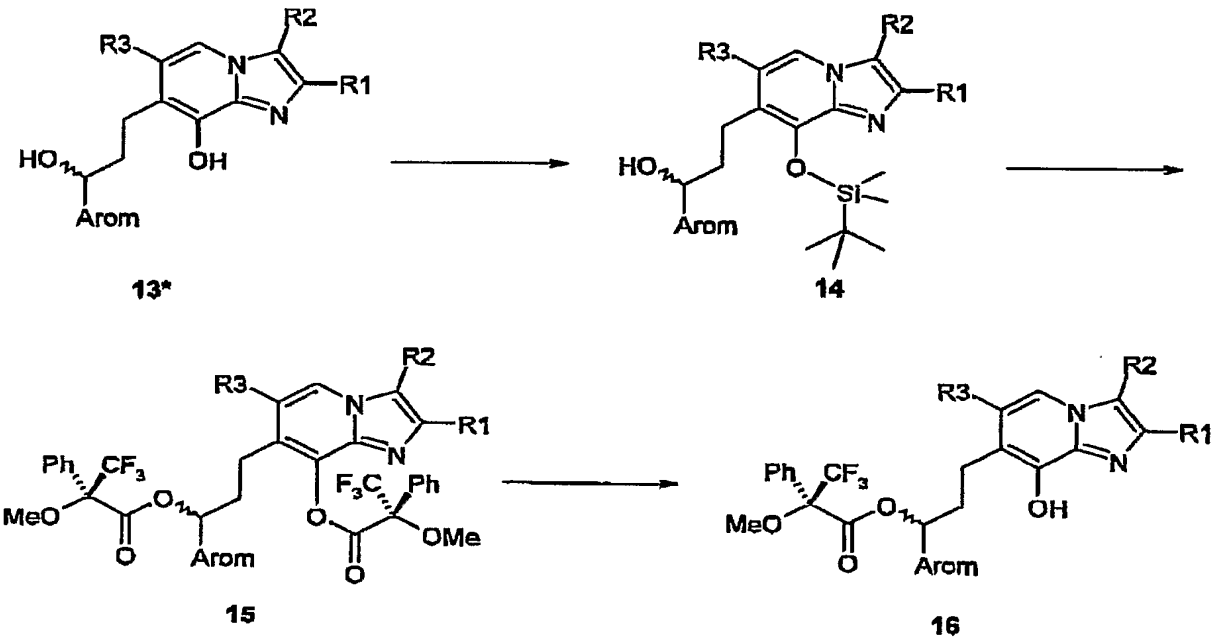
autoclave, pressurized with hydrogen (40 bar) and stirred for 19 hours at room temperature. The green solution was poured onto a mixture of saturated ammonium chloride solution (80 ml) and ethyl acetate (100 ml). The phases were separated and the aqueous phase (pH value: 8) was extracted with ethyl acetate (3 x 20 ml). The combined organic phases were washed with saturated ammonium chloride solution (2 x 20 ml) and water (20 ml), dried over sodium sulfate and concentrated under reduced pressure. The residue, a green solid (1.1 g), was purified by flash chromatography [50 g of silica gel, solvent: dichloromethane / methanol = 20:1 (v/v)] and subsequent washing with diethyl ether (10 ml). A grey solid was isolated (580 mg, 58 %) which was characterized as the pure diol 8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide. No traces of chemical impurities were visible in the ^{1}H-NMR spectrum of the compound. In order to determine optical purity and enantiomeric excess, the diol 8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide was transformed into the silyl ether 8-(*tert*-Butyl-dimethylsilanyloxy)-7-(3-hydroxy-3-phenylpropyl)-2,3-dimethyl-imidazo[1,2-a] pyridine-6-carboxylic acid dimethylamide applying the experimental procedure given below (example ii, 63 % yield). The following conditions were employed for the HPLC separation of the enantiomers: column: CHIRALPAK® AD-H 250 x 4.6 mm, 5 µm; solvent: isopropanol/hexane = 17:83 (v/v), flow rate: 1 ml/min; temperature: 35 °C. The (3*R*)-enantiomer (94.87 area-%) and the (3*S*)-enantiomer (4.97 area-%) of the silyl ether 8-(*tert*-Butyl-dimethylsilanyloxy)-7-(3-hydroxy-3-phenylpropyl)-2,3-dimethyl-imidazo[1,2-a] pyridine-6-carboxylic acid dimethylamide were eluted at retention times of 5.03 min / 5.35 min, respectively. Thus, the asymmetric catalytic hydrogenation proceeded with 90 % ee, the (3*R*)-isomer of 8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide being the major product.

^{1}H-NMR (dmso-d_6, 200 MHz): δ = 1.81 (m_c, 2 H), 2.30, 2.33 (2 s, 6 H), 2.50 (bm_c), 2.78, 2.91 (2 s, 6 H), 4.49 (t, 1 H), 7.25 (m_c, 5 H), 7.59 (s, 1 H).

IV. Configurational Analysis

The configurational assignment of the compounds of the formula 1 and 2 is based on the method described by J. A. Dale and H. S. Mosher in *J. Am. Chem. Soc.* **1973**, *95*, 512-519. The examples below serve to illustrate the method in more detail without limiting it. The configuration of further compounds of the formula 1 and 2 can likewise be analyzed in an analogous manner as shown in a general way in Scheme 5.

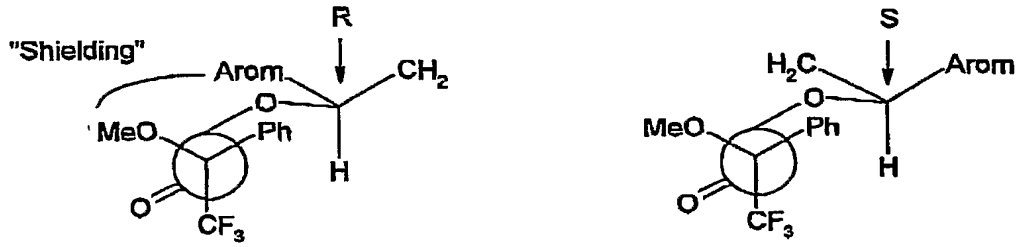
Scheme 5



It is well-known that the Mitsunobu reaction proceeds with inversion of configuration (see e. g. O. Mitsunobu *Synthesis* **1981**, 1; D. L. Hughes *Org. Prep. Proc. Int.* **1996**, *28*, 127). Specifically, when a chiral secondary alcohol is employed, the substrate undergoes an S_N2 displacement with inversion of configuration (see e. g. N. L. Dirlam, B. S. Moore, F. J. Urban *J. Org. Chem.* **1987**, *52*, 3587). Thus, the (8*S*)-enantiomer (compound of the formula 1, example 2) is derived from 8-Hydroxy-7-[(3*R*)-3-hydroxy-3-phenyl-propyl]-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide. For the configurational assignment of the enantiomeric diols of 8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide, an enantio-enriched sample obtained by catalytic hydrogenation of the ketone 8-Hydroxy-2,3-dimethyl-7-(3-oxo-3-phenyl-propyl)-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide [1.2 KO^{t}Bu, 2 mol-% $RuCl_2$[(*S*)-BINAP][(*S*,*S*)-DIPEN], 45 bar H_2, isopropanol, 80 °C, 18 h, 82 % yield] was treated with *tert*-butyldimethylsilyl chloride (scheme 5). The enantioselectivity of the catalytic hydrogenation reaction was determined by chiral HPLC separation of the resulting silyl ethers (3*S*)- and (3*R*)-8-(*tert*-Butyl-dimethylsilanyloxy)-7-(3-hydroxy-3-phenylpropyl)-2,3-dimethyl-imidazo[1,2-a] pyridine-6-carboxylic acid dimethylamide,

compounds of the formula 14 (with R1, R2 = CH_3, R3 = $(CH_3)_2N$-C(O), Arom = phenyl), (7:3 ratio of enantiomers (3*R*) : (3*S*)). Treatment of the reaction product of the formula 14 with (*S*)-(+)-MTPACl furnished the diacylated imidazopyridine of the formula 15 (R1, R2 = CH_3, R3 = $(CH_3)_2N$-C(O), Arom = phenyl). The phenolic ester group was cleaved and the diastereomeric Mosher esters of the formula 16 (R1, R2 = CH_3, R3 = $(CH_3)_2N$-C(O), Arom = phenyl) were obtained in a 7:3 ratio in accordance to the result for the enantiomeric silyl ethers of the formula 14.

Figure 1



δ (OCH_3) = 3.43 ppm

δ (OCH_3) = 3.52 ppm

Mosher and coworkers have shown that the conformation depicted in Figure 1 is highly preferred for this class of compounds. In the (3*R*)-diastereomer of the compound of the formula 16, the methoxy function is located over the Arom radical. The shielding effect of the aromatic electron cloud results in an upfield-shift of the ^{1}H-NMR signal of the methoxy group as compared to the (3*S*)-diastereomer. In the ^{1}H NMR spectrum of the diastereomeric mixture, the signals of the methoxy groups were observed at 3.43 ppm (major) / 3.52 ppm (minor), respectively. Thus, catalytic hydrogenation under the conditions reported above mainly furnishes the (3*R*)-diol of the formula 13. After Mitsunobu etherification, an enantio-enriched sample of the (8*S*)-enantiomer of the formula 1 is isolated.

Experimental Details of the Configuration Analysis

I. 8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide; prepared by asymmetric catalytic hydrogenation

The ketone 8-Hydroxy-2,3-dimethyl-7-(3-oxo-3-phenyl-propyl)-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide (2.00 g, 5.5 mmol), potassium *tert*-butylate (0.74 g, 6.6 mmol), and the hydrogenation catalyst $RuCl_2$[(*S*)-BINAP][(*S,S*)-DIPEN] (preparation of the catalyst according to the procedure given by R. Noyori and T. Ohkuma in *Angew. Chem.* **2001**, *113*, 40-75, 110 mg, 0.11 mmol, 2 mol-%) were dissolved in dry isopropanol (150 ml) which had been degassed with argon. The homogenous, brown solution was transferred into a 300 ml autoclave, pressurized with hydrogen (45 bar) and heated to 80 °C. The reaction mixture was kept at 80 °C for 18 h, cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in water (50 ml) and the pH-value of the solution was adjusted to 7.5 by addition of 2 N hydrochloric acid (2.4 ml). The aqueous phase was extracted with dichloromethane (3 x 100 ml). The pH-value was re-adjusted and the extraction was repeated two

more times. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue, a green-brown solid, was purified by flash chromatography [100 g of silica gel, solvent: dichloromethane / methanol = 15:1 (v/v)]. A grey solid was isolated (1.64 g, 82 %) which was characterized as the pure diol 8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide. No traces of chemical impurities were visible in the ^{1}H-NMR spectrum of the compound. A direct determination of the optical purity and the enantiomeric excess of the sample by chiral HPLC was not possible due to extensive peak-tailing.

^{1}H-NMR (dmso-d_6, 200 MHz): δ = 1.81 (m_c, 2 H), 2.30, 2.33 (2 s, 6 H), 2.50 (bm_c), 2.78, 2.91 (2 s, 6 H), 4.49 (t, 1 H), 7.25 (m_c, 5 H), 7.59 (s, 1 H).

ii. 8-(*tert*-Butyl-dimethylsilanyloxy)-7-(3-hydroxy-3-phenylpropyl)-2,3-dimethyl-imidazo[1,2-a] pyridine-6-carboxylic acid dimethylamide; determination of the enantiomeric excess obtained by asymmetric reduction of the ketone

For analytical purposes, the diol 8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide (200 mg, 0.54 mmol, product of the asymmetric hydrogenation described above) was dissolved in dichloromethane (10 ml). Triethylamine (110 mg, 151 µl, 1.09 mmol) and a solution of *tert*-butyldimethylsilyl chloride (179 mg, 1.19 mmol) in dichloromethane (5 ml) were added. The reaction mixture was heated to reflux for 5.25 h and was then quenched by addition of saturated ammonium chloride solution (10 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 10 ml). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. A green oil (296 mg) remained which was purified by flash chromatography (20 g of silica gel, solvent: ethyl acetate). The silyl ether 8-(*tert*-Butyl-dimethylsilanyloxy)-7-(3-hydroxy-3-phenylpropyl)-2,3-dimethyl-imidazo[1,2-a] pyridine-6-carboxylic acid dimethylamide was isolated in 73 % yield (190 mg). No impurities were visible in the ^{1}H-NMR spectrum of the colourless oil. The following conditions were employed for the determination of the enantiomeric excess by chiral HPLC: column: 2 CHIRALPAK® AD-H columns 250 x 4.6 mm, 5 µm; solvent: isopropanol/hexane = 17:83 (v/v), flow rate: 1 ml/min; temperature: 35 °C. The (3*R*)-enantiomer (68.35 area-%) and the (3*S*)-enantiomer (31.65 area-%) of 8-(*tert*-Butyl-dimethylsilanyloxy)-7-(3-hydroxy-3-phenylpropyl)-2,3-dimethyl-imidazo[1,2-a] pyridine-6-carboxylic acid dimethylamide were eluted at retention times of 9.97 min / 10.60 min, respectively. Thus, the asymmetric catalytic hydrogenation proceeded with 37 % ee.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 0.33, 0.44 (2 s, 6 H), 1.02 (s, 9 H), 2.00 (m_c, 2 H), 2.33, 2.37 (2 s, 6 H), 2.65 (m_c, 2 H), 2.88, 3.11 (2 s, 6 H), 4.58 (dd, 1 H), 7.26 (m_c, 5 H), 7.38 (s, 1 H).

iii. (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 3-(6-dimethylcarbamoyl-8-hydroxy-2,3-dimethyl-imidazo[1,2-a]pyridin-7-yl)-(1*R*,*S*)-1-phenyl-propyl ester; configurational assignment of the enantiomers of 8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide

(a) In order to determine the absolute configuration of the (3*S*)- and (3*R*)-enantiomer of 8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide, (*S*)-(+)-MTPACl (95 mg, 0.38 mmol) was dissolved in pyridine (810 µl) and carbon tetrachloride (810 µl). A solution of the (3*R*)- and (3*S*)-enantiomers of the silyl ether 8-(*tert*-Butyl-dimethylsilanyloxy)-7-(3-hydroxy-3-phenylpropyl)-2,3-dimethyl-imidazo[1,2-a]-pyridine-6-carboxylic acid dimethylamide (100 mg, 0.21 mmol, containing the two enantiomers in a 7:3 ratio) in dichloromethane (500 µl) was added. The reaction mixture was stirred for 6 hours at room temperature and was then diluted with water (5 ml) and chloroform (10 ml). The phases were separated and the aqueous phase was extracted with chloroform (2 x 10 ml). The organic phases were washed with saturated sodium chloride solution (5 ml), dried over sodium sulfate and concentrated under reduced pressure. The crude product was dried thoroughly and then purified by flash chromatography (10 g of silica gel, solvent: ethyl acetate / petrol-ether = 7:3). A yellowish oil (50 mg, 30 % yield) was isolated which was characterized as the di-astereomeric mixture of the diesters of the formula 15 with R1, R2 = CH_3, R3 = $(CH_3)_2N$-C(O) and Arom = phenyl.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 2.00-2.60 (bs), 2.34, 2.37 (2 s, Σ 10 H), 2.73 (s, 3 H), 2.87, 2.97 (2 s, Σ 3 H), 3.44, 3.48 (2 s, Σ 3 H), 3.79, 3.85 (2 s, Σ 3 H), 5.61 (bt, 1 H), 7.30 (m_c, 10 H), 7.54 (m_c, 3 H), 7.63 (s, 1 H), 8.06 (m_c, 2 H).

(*b*) A solution of the diastereomeric mixture of the diesters of the formula 15 with R1, R2 = CH_3, R3 = $(CH_3)_2N$-C(O) and Arom = phenyl (42 mg, 0.05 mmol) in deuterated chloroform was allowed to stand for 10 d at room temperature. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography [2 x 6 g of silica gel, solvent: dichloromethane / methanol = 15:1 (v/v)]. A mixture of the diastereomeric esters of the formula 16 with R1, R2 = CH_3, R3 = $(CH_3)_2N$-C(O) and Arom = phenyl (22 mg of a colourless foam) was isolated in 72 % yield. In the ^{1}H-NMR spectrum of this compound, two distinct signals for the methoxy group of the acyl moiety were visible. The chemical shift values of the signals corresponding to the major / minor enantiomer were 3.43 / 3.52 ppm.

^{1}H-NMR (dmso-d_6, 400 MHz): δ = 2.05 (bs, 1 H), 2.17 (bs, 1 H), 2.29, 2.32 (2 s, 6 H), 2.48 (bs), 2.71, 2.75 (2 s, Σ 3 H), 2.82, 2.84 (2 s, Σ 3 H), 3.43, 3.52 (2 s, Σ 3 H), 5.98 (m_c, 1 H), 7.41 (m_c, 10 H), 7.61, 7.62 (2 s, Σ 1 H).

Based on the method for configurational analysis suggested by Mosher et al. (see above), the major enantiomer of the diol 8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide as prepared above possesses (3*R*)-configuration.

Commercial utility

The compounds of the formula 1 and their salts have valuable pharmacological properties which make them commercially utilizable. In particular, they exhibit marked inhibition of gastric acid secretion and an excellent gastric and intestinal protective action in warm-blooded animals, in particular humans. In this connection, the compounds according to the invention are distinguished by a high selectivity of action, an advantageous duration of action, a particularly good enteral activity, the absence of significant side effects and a large therapeutic range.

"Gastric and intestinal protection" in this connection is understood as meaning the prevention and treatment of gastrointestinal diseases, in particular of gastrointestinal inflammatory diseases and lesions (such as, for example, gastric ulcer, peptic ulcer, including peptic ulcer bleeding, duodenal ulcer, gastritis, hyperacidic or medicament-related functional dyspepsia), which can be caused, for example, by microorganisms (e.g. Helicobacter pylori), bacterial toxins, medicaments (e.g. certain antiinflammatories and antirheumatics, such as NSAIDs and COX-inhibitors), chemicals (e.g. ethanol), gastric acid or stress situations. "Gastric and intestinal protection" is understood to include, according to general knowledge, gastroesophageal reflux disease (GERD), the symptoms of which include, but are not limited to, heartburn and/or acid regurgitation.

In their excellent properties, the compounds according to the invention surprisingly prove to be clearly superior to the compounds known from the prior art in various models in which the antiulcerogenic and the antisecretory properties are determined. On account of these properties, the compounds of the formula 1 and their pharmacologically acceptable salts are outstandingly suitable for use in human and veterinary medicine, where they are used, in particular, for the treatment and/or prophylaxis of disorders of the stomach and/or intestine.

A further subject of the invention are therefore the compounds according to the invention for use in the treatment and/or prophylaxis of the abovementioned diseases.

The invention likewise includes the use of the compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the abovementioned diseases.

The invention furthermore includes the use of the compounds according to the invention for the treatment and/or prophylaxis of the abovementioned diseases.

A further subject of the invention are medicaments which comprise one or more compounds of the formula 1 and/or their pharmacologically acceptable salts.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the pharmacologically active compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries or excipients in the form of tablets, coated tablets, capsules, suppositories, patches (e.g. as TTS), emulsions, suspensions or solutions, the active compound content advantageously being between 0.1 and 95% and it being possible to obtain a pharmaceutical administration form exactly adapted to the active compound and/or to the desired onset and/or duration of action (e.g. a sustained-release form or an enteric form) by means of the appropriate selection of the auxiliaries and excipients.

The auxiliaries and excipients which are suitable for the desired pharmaceutical formulations are known to the person skilled in the art on the basis of his/her expert knowledge. In addition to solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound excipients, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or, in particular, permeation promoters and complexing agents (e.g. cyclodextrins).

The active compounds can be administered orally, parenterally or percutaneously.

In general, it has proven advantageous in human medicine to administer the active compound(s) in the case of oral administration in a daily dose of approximately 0.01 to approximately 20, preferably 0.05 to 5, in particular 0.1 to 1.5, mg/kg of body weight, if appropriate in the form of several, preferably 1 to 4, individual doses to achieve the desired result. In the case of a parenteral treatment, similar or (in particular in the case of the intravenous administration of the active compounds), as a rule, lower doses can be used. The establishment of the optimal dose and manner of administration of the active compounds necessary in each case can easily be carried out by any person skilled in the art on the basis of his/her expert knowledge.

If the compounds according to the invention and/or their salts are to be used for the treatment of the abovementioned diseases, the pharmaceutical preparations can also contain one or more pharmacologically active constituents of other groups of medicaments, for example: tranquillizers (for example from the group of the benzodiazepines, for example diazepam), spasmolytics (for example, bietamiverine or camylofine), anticholinergics (for example, oxyphencyclimine or phencarbamide), local anesthetics, (for example, tetracaine or procaine), and, if appropriate, also enzymes, vitamins or amino acids.

To be emphasized in this connection is in particular the combination of the compounds according to the invention with pharmaceuticals which inhibit acid secretion, such as, for example, H_2 blockers (e.g. cimetidine, ranitidine), H^+/K^+ ATPase inhibitors (e.g. omeprazole, pantoprazole), or further with so-called peripheral anticholinergics (e.g. pirenzepine, telenzepine) and with gastrin antagonists with the

aim of increasing the principal action in an additive or super-additive sense and/or of eliminating or of decreasing the side effects, or further the combination with antibacterially active substances (such as, for example, cephalosporins, tetracyclines, penicillins, macrolides, nitroimidazoles or alternatively bismuth salts) for the control of Helicobacter pylori. Suitable antibacterial co-components which may be mentioned are, for example, mezlocillin, ampicillin, amoxicillin, cefalothin, cefoxitin, cefotaxime, imipenem, gentamycin, amikacin, erythromycin, ciprofloxacin, metronidazole, clarithromycin, azithromycin and combinations thereof (for example clarithromycin + metronidazole).

In view of their excellent gastric and intestinal protection action, the compounds of formula 1 are suited for a free or fixed combination with those medicaments (e.g. certain antiinflammatories and antirheumatics, such as NSAIDs), which are known to have a certain ulcerogenic potency. In addition, the compounds of formula 1 are suited for a free or fixed combination with motility-modifying drugs.

Pharmacology

The excellent gastric protective action and the gastric acid secretion-inhibiting action of the compounds according to the invention can be demonstrated in investigations on animal experimental models. The compounds of the formula 1 according to the invention investigated in the model mentioned below have been provided with numbers and their optical antipodes of the formula 2 with letters which correspond to the numbers and letters of these compounds in the examples.

Testing of the secretion-inhibiting action on the perfused rat stomach

In Table A which follows, the influence of the compounds of the formula 1 according to the invention and of their optical antipodes of the formula 2 on the pentagastrin-stimulated acid secretion of the perfused rat stomach after intraduodenal administration in vivo is shown.

Table A

No. / letters	Dose (µmol/kg) i.d.	Inhibition of acid secretion (%)
1	1	100
A	3	< 50
2	1	100
B	3	< 50

Methodology

The abdomen of anesthetized rats (CD rat, female, 200-250 g; 1.5 g/kg i.m. urethane) was opened after tracheotomy by a median upper abdominal incision and a PVC catheter was fixed transorally in the esophagus and another via the pylorus such that the ends of the tubes just projected into the gastric lumen. The catheter leading from the pylorus led outward into the right abdominal wall through a side opening.

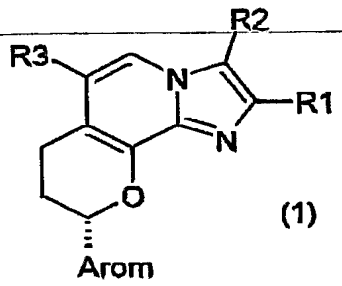
After thorough rinsing (about 50-100 ml), warm (37°C) physiological NaCl solution was continuously passed through the stomach (0.5 ml/min, pH 6.8-6.9; Braun-Unita I). The pH (pH meter 632, glass electrode EA 147; ϕ = 5 mm, Metrohm) and, by titration with a freshly prepared 0.01N NaOH solution to pH 7 (Dosimat 665 Metrohm), the secreted HCl were determined in the effluent in each case collected at an interval of 15 minutes.

The gastric secretion was stimulated by continuous infusion of 1 µg/kg (= 1.65 ml/h) of i.v. pentagastrin (left femoral vein) about 30 min after the end of the operation (i.e. after determination of 2 prelimi-

nary fractions). The substances to be tested were administered intraduodenally in a 2.5 ml/kg liquid volume 60 min after the start of the continuous pentagastrin infusion. The body temperature of the animals was kept at a constant 37.8-38°C by infrared irradiation and heat pads (automatic, stepless control by means of a rectal temperature sensor).

We claim:

1. A compound of the formula 1



(1)

in which

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl or 1-4C-alkoxycarbonyl

R2 is hydrogen, 1-4C-alkyl, halogen, 2-4C-alkenyl, 2-4C-alkynyl, hydroxy-1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxycarbonyl

R3 is hydroxy-1-2C-alkyl, 1-4C-alkoxy-1-2C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-2C-alkyl, 1-4-C-alkoxycarbonyl or the radical -CO-NR31R32,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino, morpholino radical.

Arom is a R4-, R5-, R6- and R7- substituted mono- or bicyclic aromatic radical selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furanyl (furyl), benzofuranyl (benzofuryl), thiophenyl (thienyl), benzothiophenyl (benzothienyl), thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, quinolinyl and isoquinolinyl,

where

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxyl, aryl, aryl-1-4C-alkyl, aryloxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,

R6 is hydrogen, 1-4C-alkyl or halogen and

R7 is hydrogen, 1-4C-alkyl or halogen,

where

aryl is phenyl or substituted phenyl having one, two or three identical or different substituents from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxyl and cyano,

and its salts.

2. A compound of the formula 1 as claimed in claim 1, in which

R1 is 1-4C-alkyl or 3-7C-cycloalkyl

R2 is 1-4C-alkyl, halogen, hydroxy-1-4C-alkyl, 2-4C-alkenyl or 3-7C-cycloalkyl,

R3 is the radical -CO-NR31R32,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino, morpholino radical,

Arom is a R4-, R5-, R6- and R7- substituted mono- or bicyclic aromatic radical selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furanyl (furyl), benzofuranyl (benzofuryl), thiophenyl (thienyl), benzothiophenyl (benzothienyl), thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, quinolinyl and isoquinolinyl,

where

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxyl, aryl, aryl-1-4C-alkyl, aryloxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,

R6 is hydrogen, 1-4C-alkyl or halogen and

R7 is hydrogen, 1-4C-alkyl or halogen,

where

aryl is phenyl or substituted phenyl having one, two or three identical or different substituents from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxyl and cyano,

and its salts.

3. A compound of the formula 1 as claimed in claim 1, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl, halogen, hydroxy-1-4C-alkyl or 2-4C-alkenyl,

R3 is the radical -CO-NR31R32,

where

R31 is hydrogen or 1-7C-alkyl,

R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino, morpholino radical,

Arom is a R4- and R5- substituted phenyl, furanyl (furyl), thiophenyl (thienyl) or pyridinyl,
where
R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,
R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,

and its salts.

4. A compound of the formula 1 as claimed in claim 1, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is the radical -CO-NR31R32,
where
R31 is hydrogen or 1-7C-alkyl,
R32 is hydrogen or 1-7C-alkyl,
or where
R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino, morpholino radical,

Arom is a R4- and R5- substituted phenyl, furanyl (furyl), thiophenyl (thienyl) or pyridinyl,
where
R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,
R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,

and its salts.

5. A compound of the formula 1 as claimed in claim 1, in which

R1 is 1-4C-alkyl,

R2 halogen, hydroxy-1-4C-alkyl or 2-4C-alkenyl,

R3 is the radical -CO-NR31R32,
where
R31 is hydrogen or 1-7C-alkyl,
R32 is hydrogen or 1-7C-alkyl,
or where
R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino, morpholino radical,

Arom is a R4- and R5- substituted phenyl, furanyl (furyl), thiophenyl (thienyl) or pyridinyl,
where
R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,
R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, halogen or hydroxyl,

and its salts.

6. A compound of the formula 1 as claimed in claim 1, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is the radical -CO-NR31R32,

where

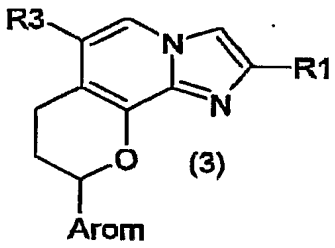
R31 is hydrogen or 1-7C-alkyl,

R32 is hydrogen or 1-7C-alkyl,

Arom is phenyl

and its salts.

7. A compound of the formula 3



(3)

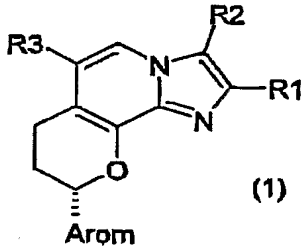
in which

R1, R3 and Arom have the meanings as indicated in claim 1

and its salts.

8. A process for the synthesis of a compound of the formula 1 as claimed in claim 1, which comprises

- converting a compound of the formula 3 as claimed in claim 7 to a racemic mixture of a compounds of the 1 as claimed in claim 1 and its optical antipode of the formula 2



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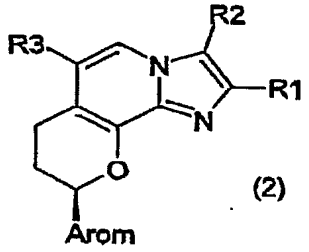


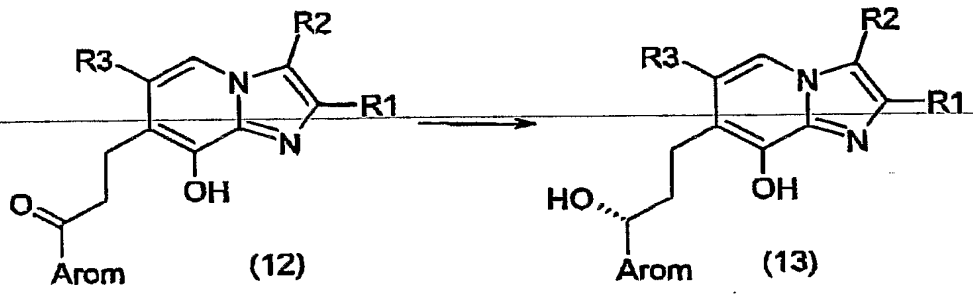
(2)

and

- separation of the compound of the formula 1 from its optical antipode of the formula 2 and
- if desired, further derivatization of the compound the formula 1 either on the stage of the racemic mixture of the compound of the formula 1 and its optical antipode of the formula 2 or after separation of the compound of the formula 1 from its optical antipode of the formula 2.

9. A process for the synthesis of a compound of the formula 1 as claimed in claim 1, which comprises

- an asymmetric reduction of a compound of the formula 12 to a compound of the formula 13



in which

R1, R2, R3 and Arom have the meanings as indicated in claim 1

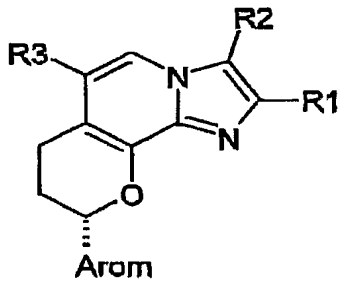
- and conversion of a compound of the formula 13 into a compound of the formula 1 or its salts.

10. A medicament comprising a compound as claimed in claim 1 and/or a pharmacologically acceptable salt thereof together with customary pharmaceutical auxiliaries and/or excipients.

11. The use of a compound as claimed in claim 1 and its pharmacologically acceptable salts for the prevention and treatment of gastrointestinal disorders.

Abstract

The invention provides compounds of the formula 1,



(1)

in which the substituents and symbols are as defined in the description. The compounds inhibit the secretion of gastric acid.